The Panel will need to consider information from multiple datasets (PREVAIL, PROTECT AF, CAP, and CAP2) in order to determine whether the totality of the data demonstrate a reasonable assurance of device safety and effectiveness of the WATCHMAN device.

Question 1: Evaluation of Device Effectiveness for Reducing Ischemic Stroke

The WATCHMAN device is a locally targeted intervention that is intended to reduce the risk of ischemic stroke and systemic embolism by preventing the embolization of thrombi formed in the left atrial appendage. The rates of ischemic stroke and systemic embolism favored the Control group in both the PROTECT AF (Tables 1 and 2 and Figure 1) and PREVAIL-only (Tables 3 and 4 and Figure 2) updated datasets.

Table 1: PROTECT AF Ischemic Stroke and Systemic Embolism Events

	WATCHMAN		Control	
Type	**N Events/ Total Pt-yrs**	**Events per 100 pt-yrs (95% CI)**	**N Events/ Total Pt-yrs**	**Events per 100 pt-yrs (95% CI)**
Stroke - Ischemic	24/1788.2	1.3 (0.86, 2.00)	10/932.8	1.1 (0.51, 1.97)
Systemic Embolism	2/1843.7	0.1 (0.01, 0.39)	0/949.0	0.0 (0.00, 0.39)
Ischemic Stroke+ System Embolism	26/1792	1.5 (0.95, 2.13)	10/933	1.1 (0.51, 1.97)

Figure 1: PROTECT AF Freedom from Ischemic Stroke/Systemic Embolism

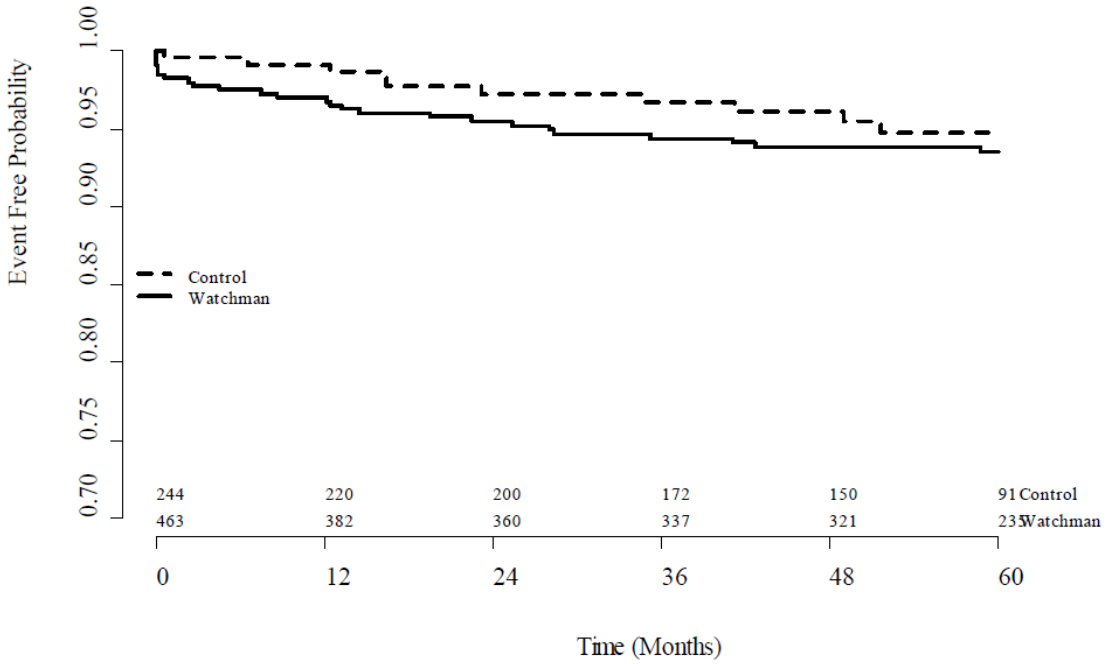

Table 2: PROTECT AF Freedom from Ischemic Stroke/Systemic Embolism

	WATCHMAN			Control		
Time Point	**N Events**	**N Cumulative Events**	**Event Free Rate (%) (95% CI)**	**N Events**	**N Cumulative Events**	**Event Free Rate (%) (95% CI)**
7-days	7	7	98.5 (96.8, 99.3)	0	0	100.0 (100.0, 100.0)
45-days	1	8	98.3 (96.5, 99.1)	1	1	99.6 (97.1, 99.9)
6-months	3	11	97.5 (95.6, 98.6)	0	1	99.6 (97.1, 99.9)
1-year	2	13	97.0 (95.0, 98.3)	1	2	99.2 (96.7, 99.8)
1.5-year	4	17	96.0 (93.7, 97.5)	3	5	97.8 (94.7, 99.1)
2-year	2	19	95.5 (93.0, 97.1)	1	6	97.3 (94.1, 98.8)
3-year	4	23	94.4 (91.7, 96.3)	1	7	96.7 (93.3, 98.4)
4-year	2	25	93.8 (91.0, 95.8)	1	8	96.1 (92.4, 98.1)
5-year	1	26	93.5 (90.6, 95.6)	2	10	94.8 (90.5, 97.2)

Table 3: PREVAIL-only Ischemic Stroke and Systemic Embolism Events

	WATCHMAN		Control	
	N Events/ Total pt-yrs	**Rate* (95% CI)**	**N Events/ Total Pt-yrs**	**Rate* (95% CI)**
Stroke - Ischemic**	13/564.9	2.30 (1.23, 3.94)	1/298.1	0.34 (0.01,1.87)
Systemic Embolism	1/576.9	0.17 (0.004, 0.97)	0/300.2	0.00 (0.00,1.23)
Ischemic Stroke + Systemic Embolism***	14/566	2.47 (1.35, 4.15)	1/298	0.34 (0.008, 1.87)

*Rate per 100 pt-yrs = Event rate per 100 patient-years
** Assuming Poisson distribution, ischemic stroke rate ratio control vs. device = 0.15, p-value = 0.044
*** Ischemic stroke/systemic embolism rate ratio control vs. device = 0.14, p-value = 0.027

Figure 2: PREVAIL-only Freedom from Ischemic Stroke or Systemic Embolism

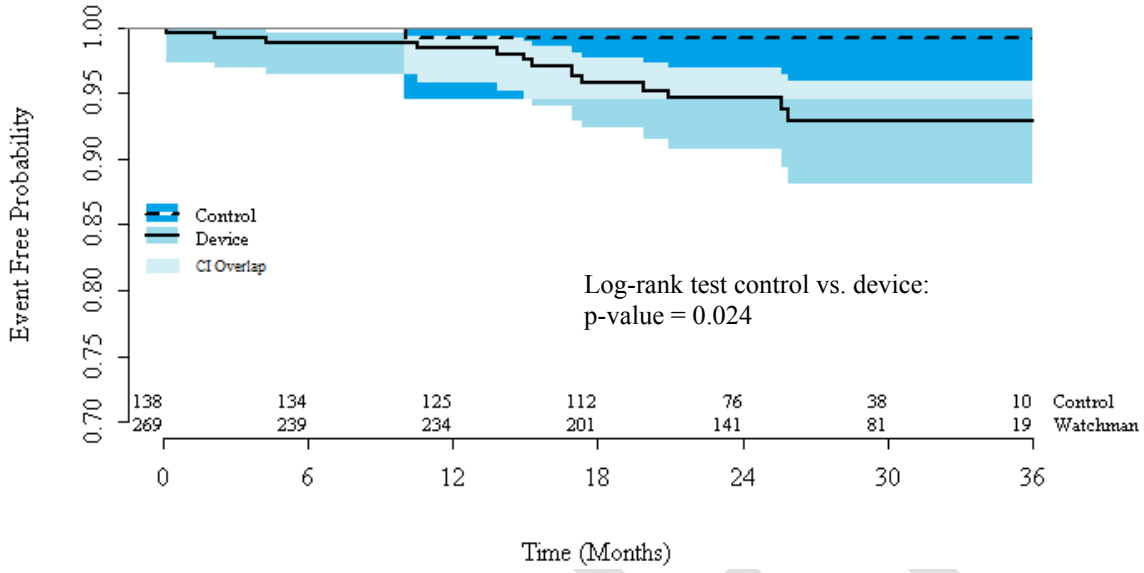

Table 4: PREVAIL-only Freedom from Ischemic Stroke or Systemic Embolism

	WATCHMAN			Control		
Time Point	**N Events**	**N Cumulative Events***	**Event Free Rate (%) (95% CI)**	**N Events**	**N Cumulative Events***	**Event Free Rate (%) (95% CI)**
Baseline	0	0	100.0 (100.0, 100.0)	0	0	100.0 (100.0, 100.0)
7-days	1	1	99.6 (97.4, 99.9)	0	0	100.0 (100.0, 100.0)
45-days	0	1	99.6 (97.4, 99.9)	0	0	100.0 (100.0, 100.0)
6-months	2	3	98.8 (96.4, 99.6)	0	0	100.0 (100.0, 100.0)
1-year	1	4	98.4 (95.8, 99.4)	1	1	99.2 (94.5, 99.9)
18-months	6	10	95.8 (92.3, 97.7)	0	1	99.2 (94.5, 99.9)
2-year	2	12	94.6 (90.7, 96.9)	0	1	99.2 (94.5, 99.9)
3-year	2	14	92.9 (88.1, 95.9)	0	1	99.2 (94.5, 99.9)

* 2:1 Randomization Device to Control

In addition, the second primary endpoint in PREVAIL (18-month rate of ischemic stroke and systemic embolism, excluding events occurring within 7 days following randomization) was designed to support this mechanism of action beyond the peri-procedural period, and non-inferiority of this endpoint was not met based on the updated June 2014 dataset, incorporating the PROTECT AF informative prior (Table 5). In this case, the posterior probability of non-inferiority is 89.5%. Based on PREVAIL data only, the posterior probability of non-inferiority is only 48.8%.

Table 5: PREVAIL Second Primary Endpoint

Bayesian Approach	Device 18 Month Rate	Control 18 Month Rate	18 Month Rate Difference (95% CrI)**	Post. Prob. of Non-Inferiority**	Non-Inferiority Criteria Met? (Yes/No)
PREVAIL June 2014 + PROTECT AF prior	0.0294	0.0131	0.0163 (-0.0023, 0.0342)	89.5%	No
PREVAIL-only June 2014	0.033	0.004	0.0284 (0.0097, 0.0499)	48.8%	No

*The rate difference non-inferiority criterion is that the upper bound of the equitailed 2-sided 95% CrI for rate difference is less than 0.0275. This is equivalent to posterior probability of non-inferiority (that rate difference < 0.0275) is at least 97.5%.

Please comment on the clinical significance of the results from PROTECT AF and PREVAIL, and discuss whether the WATCHMAN device is sufficiently comparable to warfarin in reducing the risk of ischemic stroke in patients with non-valvular AF.

Question 2: Evaluation of Hemorrhagic Stroke

The results of the PROTECT AF trial suggest that the WATCHMAN device offers an important benefit compared with warfarin therapy by lowering the risk of hemorrhagic stroke (Table 6). This signal of reduced risk of hemorrhagic stroke in WATCHMAN subjects was not observed in PREVAIL. This potential benefit is particularly important as hemorrhagic stroke is often associated with significant disability or death, and an assessment of hemorrhagic stroke risk is a key component of the assessment of the benefit-risk profile of the WATCHMAN device compared with warfarin therapy.

Table 6: Hemorrhagic Stroke in PROTECT AF and PREVAIL-only

	WATCHMAN N events (rate per 100 pt-yrs) (95% CI)	Control N events (rate per 100 pt-yrs) (95% CI)
PREVAIL-only	2 (0.35) (0.04, 1.25)	2 (0.67) (0.08, 2.41)
PROTECT AF	3 (0.2) (0.03, 0.48)	10 (1.1) (0.52, 1.98)

*2:1 device:control randomization

However, the robustness of this signal in PROTECT AF is limited by:

- The hemorrhagic stroke rate in the PROTECT AF Control group was higher than expected and at least 2-fold higher compared to the warfarin groups in contemporary anticoagulation trials;

- Circumstances regarding PROTECT AF Control subjects who were adjudicated as having hemorrhagic stroke, including:
    - non-use of warfarin in one subject,
    - absence of imaging confirmation in one subject,
    - concomitant use of antiplatelet agents in several subjects, and
    - events associated with trauma in several subjects.

Please comment on the potential benefit and the magnitude of the benefit of the WATCHMAN device to reduce the risk of hemorrhagic stroke compared to warfarin.

Question 3: Updated PREVAIL First and Second Primary Endpoint Results

The sponsor provided an updated dataset for PREVAIL (June 2014 dataset) that includes substantially more subject follow-up than the previous January 2013 dataset. In the updated Bayesian analysis that combines the PREVAIL data with 50% discounted data from PROTECT AF, the WATCHMAN device continues to not meet the non-inferiority criteria for the first primary endpoint (Table 7), and no longer meets the non-inferiority criteria for the second primary endpoint (Table 8).

Table 7: PREVAIL First Primary Endpoint

Bayesian Approach	Device 18 Month Rate	Control 18 Month Rate	18 Month Rate Ratio (95% CrI)	Posterior Prob. of non-inferiority	Rate Ratio Non-Inferiority Criteria*	Criteria Met? (Yes/No)
PREVAIL June 2014 + PROTECT AF prior	0.065	0.057	1.21 (0.69,2.05)	92.60%	95% CrI <1.75 (Post.Prob. ≥97.5%)	No
PREVAIL only June 2014	0.067	0.041	1.84 (0.803, 3.851)	54.4%	95% CrI <1.75 (Post.Prob. ≥97.5%)	No

*The non-inferiority criterion is that the upper bound of the equitailed 2-sided 95% CrI for the rate ratio is <1.75. This is equivalent to a posterior probability of non-inferiority that rate ratio is at least 97.5%.

Table 8: PREVAIL Second Primary Endpoint

Bayesian Approach	Device 18 Month Rate	Control 18 Month Rate	18 Month Rate Difference (95% CrI)**	Post. Prob. of Non-Inferiority**	Non-Inferiority Criteria Met? (Yes/No)
PREVAIL June 2014 + PROTECT AF prior	0.0294	0.0131	0.0163 (-0.0023, 0.0342)	89.5%	No
PREVAIL only June 2014	0.033	0.004	0.0284 (0.0097, 0.0499)	48.8%	No

**The rate difference non-inferiority criterion is that the upper bound of the equitailed 2-sided 95% CrI for rate difference is less than 0.0275. This is equivalent to posterior probability of non-inferiority (that rate difference < 0.0275) is at least 97.5%.

An increasing divergence between the results of PROTECT AF and PREVAIL is present, and statistically, the results of these two studies come from significantly separate distributions, which makes combining the data from PROTECT AF and PREVAIL in a Bayesian analysis problematic. Moreover, without incorporating the PROTECT AF informative prior and based on PREVAIL data only, the posterior probability of non-inferiority for the first primary endpoint is only 54.4% and for the second primary endpoint is only 48.8% (see Tables 7 and8).

Please comment on the clinical significance of the Bayesian analysis results and the failure of the WATCHMAN device to meet both the PREVAIL first and second primary endpoints.

Question 4: Evaluation of Major Bleeding Events

A potential benefit of the WATCHMAN device compared to warfarin is a reduction in long-term bleeding complications associated with the use of chronic anticoagulation therapy. Although the WATCHMAN studies were not designed to specifically assess bleeding complications, a clinically important reduction in long-term bleeding rates in WATCHMAN vs. warfarin subjects would support this potential benefit. As expected with most invasive procedures, bleeding events in the WATCHMAN group in PREVAIL-only and PROTECT AF were clustered in the peri-procedural period. Late (>6 months post-randomization) bleeding rates favored the WATCHMAN group in both PROTECT AF (Table 9) and PREVAIL-only (Table 10). However, there was no overall advantage of the WATCHMAN device vs. warfarin with respect to bleeding.

Table 9: PROTECT AF First Major Bleeding Events

Event	WATCHMAN		Control	
	N Events/ Subjects (%)	Rate (N Events/ Total Pt-Yrs) (95% CI)	N Events/ Subjects (%)	Rate (N Events/ Total Pt-Yrs) (95% CI)
Major bleeding*	50/463 (10.8%)	2.9 (50/1743.4) (2.2,3.8)	29/244 (11.9%)	3.2 (29/904.9) (2.2,4.6)
Procedure related major bleeding	28/463 (6.0%)	-	-	-
Non-procedure related major bleeding	24/463 (5.2%)	1.3 (24/1803.7) (0.9,2.0)	29/244 (11.9%)	3.2 (29/904.9) (2.2,4.6)
0-45 days	5/463 (1.1%)	9.2 (5/54.6) (3.8,22.0)	2/244 (0.8%)	6.7 (2/29.7) (1.7, 27.0)
45 days - 6 months	4/431 (0.9%)	2.6 (4/153.6) (1.0, 6.9)	4/239 (1.7%)	4.6 (4/87.8) (1.7,12.1)
Beyond 6 months	15/397 (3.8%)	0.9 (15/1595.5) (0.6, 1.6)	23/228 (10.1%)	2.9 (23/787.5) (1.9, 4.4)

*2:1 Randomization Device to Control

Table 10: PREVAIL-only First Major Bleeding Events

Event	WATCHMAN		Control	
	N Events/ Subjects (%)	Rate (N Events/ Total Pt-Yrs) (95% CI)	N Events/ Subjects (%)	Rate (N Events/ Total Pt-Yrs) (95% CI)
Major bleeding*	29/269 (10.8%)	5.5 (29/531.1) (3.8,7.9)	14/138 (10.1%)	5.0 (14/282.1) (2.9,8.4)
Procedure related major bleeding	12/269 (4.5%)	-	-	-
Non-procedure related major bleeding	20/269 (7.4%)	3.6 (20/550.1) (2.3,5.6)	14/138 (10.1%)	5.0 (14/282.1) (2.9,8.4)
0-45 days	8/269 (3.0%)	25.0 (8/31.9) (12.5,50.1)	0/138 (0.0%)	0.0 (0/16.9) (0.0,0.0)
45 days - 6 months	7/269 (2.6%)	7.9 (7/88.6) (3.8,16.6)	3/138 (2.2%)	6.0 (3/50.4) (1.9,18.5)
Beyond 6 months	5/269 (1.9%)	1.2 (5/429.6) (0.5,2.8)	11/138 (8.0%)	5.1 (11/214.8) (2.8,9.2)

*2:1 Randomization Device to Control

Please comment on the clinical significance of the major bleeding events.

Question 5: Proposed Indications For Use

The sponsor has proposed the following intended use and indications for use:

Intended Use

"The WATCHMAN LAAC Device is a percutaneous, transcatheter closure device intended for non-surgical closure of the left atrial appendage. In considering the use of the WATCHMAN LAAC Device, the benefits and risks of the device and the rationale for an alternative to chronic warfarin therapy should be taken into account."

Indications For Use

"The WATCHMAN LAAC Device is indicated to prevent thromboembolism from the left atrial appendage. The device may be considered for patients with non-valvular atrial fibrillation who, based on $CHADS_2$ or CHA_2DS_2-VASc scores, would be recommended for warfarin therapy to reduce the risk of stroke and systemic embolism."

Please comment on the Intended use and Indications For Use statements.

Question 6: Evaluation of the Totality of the Data from the WATCHMAN trials (Overall Benefit/Risk Assessment)

The sponsor has presented comprehensive data from two randomized controlled trials (PROTECT AF and PREVAIL) and two continued access registries (CAP and CAP2). Based on the totality of the data, do the probable benefits of the WATCHMAN device outweigh the probable risks? In answering this question, please comment on the following:

a. Both PROTECT and PREVAIL show higher rates of ischemic stroke in the WATCHMAN group vs. control group. In patients with non-valvular atrial fibrillation, it is presumed that embolism from the left atrial appendage (LAA) is the primary etiology for ischemic stroke. Do the results of PREVAIL and PROTECT AF support the central role of thromboembolism from the LAA in the pathogenesis of ischemic stroke in patients with non-valvular atrial fibrillation? Please comment on the relative effectiveness of a local (WATCHMAN) vs. systemic (warfarin) therapy.
b. Do the safety and effectiveness results from PROTECT AF and PREVAIL indicate that the WATCHMAN device is a clinically acceptable alternative to warfarin therapy?

Question 7: Labeling

The sponsor provided draft labeling in the panel pack.

Please discuss whether the proposed labeling is acceptable or whether modifications are recommended.